



The Sixth Sense

In his article, "Neurogenic Inflammation and Sensitivity to Environmental Chemicals" (101:234–238), Meggs speculates that neuropeptide mediators of inflammation may be responsible for sick building syndrome and multiple chemical sensitivity syndrome (MCS). He invokes a novel sixth sense, the "common chemical sense," in the noses of such patients. Meggs's speculations greatly exceed the scientific knowledge of the functions of neuropeptides. He seems to accept that these clinical conditions actually exist, although he acknowledges that MCS "remains highly controversial." In fact, there is a substantial body of literature (1–9) that these syndromes are largely psychogenic and are exploited by "alternative medicine" practitioners and quacks who ignore the distinction between speculation like Meggs's and proven fact, and who disregard the need for proof before clinical implementation. The American Medical Association Council on Scientific Affairs believes that multiple chemical sensitivity should not be considered a recognized clinical syndrome (10).

We appreciate Meggs's call for more scientific research into these matters. In the meantime, we hope he is not providing more grist for the quacks' mill.

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Pesticides on Food

On page 390 of the October issue of *EHP* (volume 101, number 5), there is a graph that purports to show the intake of pesticides by children in milligrams per kilogram per day. I think you owe a prominent correction/explanation to your readers. The original figure in the National Academy of Sciences report (figure 5-1, p. 172) shows that this is intake of food, not pesticide residue. The only point of the figure is that infants eat more of certain commodities than do adults on a body weight basis. If there is residue present, and if it survives processing, then they would get a correspondingly higher exposure. However, the situation is nothing like you imply.

Furthermore, I could not find any place in the report that says children consume 60 times more fruit than adults. Table 5-5 of the NAS report (p. 183) shows that apple juice may be consumed by non-nursing infants at 16 times the national average (again, relative to body weight). For 1–6 year olds, the factor is 3 or less for most all foods.

Finally, while it is true that concern about this report generated much activity within Congress and several federal agencies, a careful reading of the actual report will show that the concerns are largely theoretical in nature. Improvements are desired in consumption data, toxicity testing, overall regulatory approach, etc. There is nothing in the report, despite quotes to the contrary, that demonstrates that the food supply is unsafe for children or any other subset of the population.

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Editor's Note: The caption for the graph on page 390 of volume 101 refers to infant intake of pesticides on raw agricultural commodities, but the graph shows only amounts of food intake in proportion to body weight, not pesticide residues. We regret any confusion resulting from this caption.

Heterocyclic Amine-induced Cancer and Myocardial Lesions in Nonhuman Primates

Two articles in this issue from Adamson and co-workers (p. 190) describe the effects of feeding monkeys carcinogens formed during the cooking of food derived from animal muscle. In the first paper the frequency and descriptive pathology is reported for 2-amino-3-methylimidazo[4,5-f]quinoline (IQ)-induced liver tumors. In the second paper, a histopathological study of perfusion-fixed hearts of tumor-bearing monkeys showed a variety of myocardial lesions with exposure to IQ.

The major impact of this work is that a nonhuman primate species, the cynomolgus monkey, develops liver tumors after exposure to a heterocyclic amine that is ubiquitous in our cooked food supply (1,2). Not only do the monkeys under test get tumors, but 43 months was the average latent period for the high-dose animals and is equivalent to 15–25% of the animals' life span—a very quick response.

An important question arises from this research: Do the high doses (10 and 20 mg/kg) used chronically in these experiments relate to human exposures, and if not, are the results still significant? Humans eating well-done muscle-derived meats consume 10,000–100,000 times less material daily per kilogram of body weight than do the monkeys (3). There are a number of studies that attempt to answer this question about high-dose extrapolation. They suggest that at 104–106 times lower doses than used in the feeding studies discussed here, heterocyclic amines survive the acid in the stomach, are taken up by the bloodstream from the intestine, and are metabolized by the liver cytochrome P450-A metabolizing enzymes (4,5). The *N*-hydroxy metabolites are then either reactive in the liver after further conjugation to form DNA adducts and presumably liver tumors or are found as DNA adducts in numerous nonhepatic tissues where the conjugation reactions probably occur locally (6). The question then is do these reactions happen when the reactant is at 10,000 times lower concentration? Apparently, the answer is yes. In specific rodent experiments conducted over many orders of magnitude of dose, DNA binding for these compounds appears linear down to the levels found in a single hamburger (7). The data suggests that repair of DNA damage (heterocyclic amine adducts)

does not improve even at extremely low doses.

Another important question considering the cost of both animal care and of chemicals for feeding large animals is: Are nonhuman primates a reliable model for making extrapolations to humans? This is a difficult assessment because humans differ in so many processes including inducibility and expression of specific cytochrome P450 enzymes and various phase II conjugation reactions, so that even a closely related animal species may not make any better model for a specific individual. Of course other factors are also important for carcinogenesis and these also differ among individuals, so selection of the proper species to compare to the diverse human population for assessment of a complex phenomenon like cancer induction is truly difficult. Clearly, in the case of the cynomolgus monkey, an extremely sensitive model was found for induction of liver cancer by heterocyclic amines.

In the second paper, Thorgeirsson et al. examine cardiac lesions in the same monkeys receiving chronic feeding of IQ. Eight of 10 monkeys showed focal myocardial lesions. This included myocyte necrosis and interstitial fibrosis as seen by light microscopy and disruption of mitochondrial architecture and clumping of nuclear chromatin by electron microscopy analysis. The finding that heart lesions are associated with chronic feeding of chemicals common in our diet is most intriguing. Most associations of heart disease with diet are centered around fat intake. These heterocyclic amines are covariates in these studies and will be present in the diet in varying amounts whenever the fat is derived from cooked animal muscle foods (chicken, beef, pork, lamb, fish, etc.). Thus, the heterocyclic amine effects will be difficult to separate from fat effects in epidemiology

studies. The finding of cardiac toxicity with IQ exposure needs further study to evaluate its significance for heart disease. Additional questions also arise concerning the mechanism of cardiac damage versus carcinogenesis: Are the same active intermediates (possibly nitrenium ions) thought to be important in mutation and cancer also important in the heart toxicity, or are entirely different intermediates or even the parent compound responsible for the damage? It is interesting that compounds closely related in structure (benzimidazoles) are potential heart medications (8,9), at least suggesting that cardiac activity for these types of compounds is more general and not specific for the food-derived heterocyclic amines.

In conclusion, ubiquitous carcinogens in our diet appear to be potent liver carcinogens in nonhuman primates. Whether these experiments done at high doses can be directly extrapolated to humans needs to be answered. Cardiac toxicity is a new finding for these compounds and opens major questions about the role of heterocyclic amines in heart disease. Epidemiologic studies may well support such a causal relationship, and, in fact, heterocyclic amines give both the cancer induction and cardiac toxicity "biological plausibility," whereas fat is harder to explain as a causative agent.

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Editor's Note: Felton's commentary was invited by Adamson and co-workers.

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